Peralta, G., Fuertes, E., Granell, R., Mahmoud, O., Roda, C., Serra, I., Jarvis, D., Henderson, J., & Garcia-Aymerich, J. (2019). Childhood Body Composition Trajectories and Adolescent Lung Function: Findings from the ALSPAC Study. *American Journal of Respiratory and Critical Care Medicine*, *200*(1), 75-83. https://doi.org/10.1164/rccm.201806-1168OC

Childhood body composition trajectories and adolescent lung function: Findings from the ALSPAC study

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AUTHOR'S CONTRIBUTIONS

GPP and JGA prepared the first draft of the paper. GPP, IS and JGA had full access to the data and carried out statistical analysis. JH and RG contributed to data collection. All authors (i) provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, (ii) revised the manuscript for important intellectual content, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work. JGA had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

FUNDING

The present analyses are part of the Ageing Lungs in European Cohorts (ALEC) Study (www.alecstudy.org), which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 633212. The content of this article reflects only the authors' views, and the European Commission is not liable for any use that may be made of the information contained therein.

The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf).

Specifically, grants from Wellcome Trust and MRC (076467/Z/05/Z and G0401540/73080) supported the collection of body composition and lung function data at 15 years.

Elaine Fuertes is supported by a Marie Skłodowska-Curie Individual Fellowship (H2020-MSCA-IF-2015; proposal number 704268). Célina Roda is the recipient of a European

Respiratory Society Fellowship (RESPIRE3-201703-00127, under H2020 - Marie Skłodowska-Curie actions COFUND).

SHORT RUNNING TITLE

Childhood body composition and lung function

DESCRIPTOR NUMBER:

1.17 Epidemiology (Pediatric): Risk Factors

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Previous studies have shown inconsistent results regarding the association of overweight/obesity with lung function in children and adolescents, likely because most have defined overweight/obesity using the body mass index (BMI). However, the BMI does not distinguish between different components of body weight (e.g. fat mass and lean body mass). The few studies that have assessed the role of body composition on lung function in children and adolescents are all cross-sectional, based on specific populations (asthmatics, obese children, cystic fibrosis) and most did not consider the role of relevant confounders, such as previous lung function levels, pubertal status, physical activity and diet.

What This Study Adds to the Field

This longitudinal study uses data from a large population-based birth cohort with repeated objective measures of body composition and information on numerous relevant confounders to show that higher lean body mass during childhood and adolescence is associated with higher levels of FEV_1, FVC and FEF_{25-75} at 15 years and with higher growth rates of these parameters from 8 to 15 years. Higher fat mass was associated with lower levels and growth

rates of FEV_1 and FEF_{25-75} only in boys and lower levels of FEV_1/FVC in both sexes. Our study highlights the importance of assessing body composition, and not just BMI, when studying the respiratory health effects of body weight in children and adolescents.

ONLINE DATA SUPPLEMENT

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

WORLD COUNT

3,143

ABSTRACT

Rationale: Body composition changes throughout life may explain the inconsistent associations reported between body mass index (BMI) and lung function in children.

Objectives: To assess the associations of body weight and composition trajectories from 7 to 15 years with lung function at 15 years and lung function growth between 8 and 15 years.

Methods: Sex-specific BMI, lean body mass index (LBMI) and fat mass index (FMI) trajectories were developed using Group-Based Trajectory Modeling on data collected at least twice between 7 and 15 years from 6,964 children (49% boys) in the UK Avon Longitudinal Study of Parents and Children birth cohort. Associations of these trajectories with post-bronchodilation lung function parameters at 15 years and with lung function growth rates from 8 to 15 years were assessed using multivariable linear regression models, stratified by sex, in a subgroup with lung function data (n=3,575).

Measurements and Main Results: For all body mass measures we identified parallel trajectories that increased with age. There was no consistent evidence of an association between the BMI trajectories and lung function measures. Higher LBMI trajectories were associated with higher levels and growth rates of FVC, FEV_1, and FEF_{25-75} in both sexes (e.g. boys in the highest LBMI trajectory had on average a 0.62L [95%CI: 0.44; 0.79, p-trend<0.0001] higher FVC at 15 years than boys in the lowest trajectory). Increasing FMI trajectories were associated with lower levels and growth rates of FEV_1 and FEF_{25-75} only in boys and lower levels of FEV_1/FVC in both sexes.

Conclusions: Higher lean body mass during childhood and adolescence is consistently associated with higher lung function at 15 years in both sexes, whereas higher fat mass is associated with lower levels of only some lung function parameters.

Abstract word count: 284

Key words: ALSPAC, children, epidemiology, respiratory health

INTRODUCTION

Lung function is a powerful marker of overall health and a significant predictor of future morbidity and mortality in the general population (1). As lung function levels in childhood predict adult lung function, identifying factors that influence the development of lung function in childhood is important. Given the current global increase of childhood overweight and obesity, several studies have assessed their associations with lung function, but findings are inconsistent. Some studies report a positive association of overweight and obesity, as measured by body mass index (BMI), with lung function, while others show a negative association (2–8). An important limitation of these studies is that they did not distinguish between lean body mass and fat mass, both of which contribute to the composite measure BMI.

Some studies have examined body composition measures in relation to lung function, but they were all cross-sectional, most focused on specific populations (cystic fibrosis, obese or asthmatic children) and most did not consider pubertal status, physical activity or diet as relevant confounders (9–16). Furthermore, they only considered measurements at a single time point, and did not capture changes in the proportion of the different components of body weight (e.g., fat mass, lean body mass, bone mass) that occur over time and vary with sex (17).

Here we assess the association of body weight and composition trajectories, defined using repeated anthropometric and dual-energy X-ray absorptiometry (DXA) scanner measures taken from age 7 to 15 years, with lung function at 15 years and lung function growth between 8 and 15 years, using data from the UK population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. This approach overcomes the limitations of previous research.

Some of the results of this study have been previously reported in the form of an abstract to the European Respiratory Society annual congress (18).

METHODS

Complete details are provided in the online supplement.

Study population

We used data from the 14,305 singleton births recruited in the population-based UK ALSPAC birth cohort, previously described (19, 20). For the identification of body weight and composition trajectories, we included children with at least two repeated measures of body weight and composition between the ages of 7 and 15 years (n=6,964). Children who additionally had lung function measures at age 15 years were used to evaluate associations of body weight and composition trajectories with lung function measures at 15 years (n=3,575) (see Figure E1in the online supplement).

The ALSPAC Ethics and Law Committee and the Local Research Ethics Committees gave ethical approval. All participants and their parents/guardians provided written informed consent.

Measures

Body weight, height and composition were assessed following standardised procedures (21). Weight and height were measured every year from age 7 to 15 years. Body composition (total lean body mass, total fat mass, and total bone mass) was measured using a Lunar Prodigy DXA scanner at age 9, 11, 13, and 15 years. BMI, lean body mass index (LBMI) and fat mass index (FMI) were calculated by dividing body weight, total lean body mass and total fat mass (kg) by height (m) squared, respectively.

Lung function was measured by spirometry at 8 and 15 years (Vitalograph 2120; Vitalograph, Maids Moreton, United Kingdom) according to American Thoracic Society standards (22). At 15 years, lung function was measured before and after bronchodilation with salbutamol. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow at 25% and 75% of FVC (FEF_{25-75}) were obtained and the FEV_1/FVC ratio was calculated. The outcomes of the analysis were: post-bronchodilation lung function measures at 15 years and rate of lung function growth from age 8 to 15 years (calculated as (pre-bronchodilation lung function at 15 years – pre-bronchodilation lung function at 8 years)/time of follow-up in years).

We collected information, at different time points, on maternal social class, birthweight, gestational age, breastfeeding, tobacco exposure (during pregnancy, childhood and first hand), total dietary energy intake, physical activity (by accelerometer), asthma doctor-diagnosis and pubertal status.

Statistical analysis

We conducted all analyses stratified by sex as body weight and composition as well as lung function have been found to differ across sexes.

We identified BMI trajectories by applying a Group-Based Trajectory Modeling approach (23) using yearly data from ages 7 to 15 years, and LBMI and FMI trajectories using data from ages 9, 11, 13 and 15 years. As the distribution of BMI and FMI was right-skewed, we applied the natural log-transformation to all body weight and composition measures prior to the identification of the trajectories. The assigned trajectory was used as the exposure variable in all subsequent analyses.

Associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years and lung function growth rates from age 8 to 15 years were examined using multivariable linear regression. The final multivariable models included

adjustments for maternal social class, maternal smoking during pregnancy, birth weight, any breastfeeding, pubertal status as well as age and height at 15 years. We additionally adjusted all models for lung function levels at 8 years to reduce potential reverse causality. The models for the LBMI and FMI trajectories were also mutually adjusted.

We conducted several sensitivity analyses to assess the sensitivity of our estimates to varying assumptions regarding selection bias, information bias and confounding (see online supplement).

All analyses were conducted using Stata/SE 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Characteristics of study sample

We included 6,964 children (49.0% boys) in the identification of the body weight and composition trajectories. These children were more likely to be girls, have a higher socio economic status, a higher birth weight, a higher proportion of breastfeeding, and lower maternal smoking exposure than the children not included in the present analysis but participating in ALSPAC. Additionally, boys had lower LBMI and girls had lower BMI at 9 years when compared to the children not included in our analysis (see Table E1 in the online supplement). A subset of the included children with available spirometry was used to analyze the associations of body weight and composition trajectories with lung function at 15 years (n=3,575, 47.2% boys). The children in this subgroup were more likely to be girls and have a higher socio-economic status, a higher proportion of breastfeeding, and lower maternal smoking exposure than those not included, but they did not differ in terms of body weight and composition trajectories or in baseline lung function measures (see Table E2 in the online supplement).

Table 1 shows the main characteristics of the sample subset used in the association analysis with lung function. Approximately half of the mothers had a high social class and around 16% smoked during pregnancy. Boys had significantly higher lung function levels (FVC, FEV_1, and FEF_{25-75}) at 8 and15 years and higher lung function growth between 8 and 15 years than girls. Figure 1 and table 2 show the body weight and composition characteristics of the children across ages. Body weight was composed mainly of lean body mass at all ages for both boys and girls. The amount of lean body mass and fat mass changed over time, although this pattern differed by sex. Boys had lower BMI and FMI, but higher LBMI, than girls at all ages.

Body weight and composition trajectories

In both boys and girls, we identified four parallel BMI trajectories from 7 to 15 years. For both sexes, BMI increased with age (Figure 2 and Table E3 in the online supplement). According to the WHO reference cut-offs (24), we labelled these trajectories as 'normal-low', 'normal-high', 'overweight', and 'obese'. In boys, the median BMI increased from 14.6 kg/m^2 at age 7 years to 18.3 kg/m^2 at age 15 years in the 'normal-low' BMI trajectory and from 20.1 kg/m^2 at age 7 years to 27.7 kg/m^2 at age 15 years in the 'obese' BMI trajectory (see Table E3 in the online supplement).

For LBMI, we identified four parallel trajectories from age 9 to 15 in both sexes (Figure 2 and Table E4 in the online supplement). According to reference curves for body composition in children (25), we labelled these trajectories as 'low', 'medium-low', 'medium-high', and 'high'. Median LBMIs were consistently greater in boys than girls for all trajectories. Also, the increase per year of LBMI was steeper in boys than girls, specifically between age 11 and 15 years.

For FMI, we identified four parallel trajectories from age 9 to 15 in both sexes, which we labelled ‘low’, ‘medium-low’, ‘medium-high’ and ‘high’(25) (Figure 2 and Table E5 in the online supplement). Median FMIs were consistently greater in girls than boys for all trajectories. In boys, FMI levels consistently increased from age 9 to 11 years and then slightly declined from age 11 years onwards. In girls, FMI consistently increased up to 15 years in all trajectories.

Associations of body weight and composition trajectories with post-bronchodilation lung function at 15 years

Adjusted associations between the BMI trajectories and post-bronchodilation lung function measures at age 15 years were inconsistent. Significant associations were only apparent for some trajectories and some lung function parameters (Figure 3 and Table E6 in the online supplement).

Both boys and girls in the highest LBMI trajectories had higher FVC, $FEV_{1,}$ and FEF_{25-75}. The association between the LBMI trajectories and these lung function variables exhibited a linear dose-response pattern (e.g. boys in the ‘medium-low’, ‘medium-high’, and ‘high’ LBMI trajectory groups had on average a 0.24L 95%CI [0.09; 0.39], 0.44L [0.29; 0.59], and a 0.62L [0.44; 0.79] higher FVC respectively than boys in the ‘low’ LBMI trajectory [p-trend<0.0001]). We did not find any statistically significant association between the LBMI trajectories and the FEV_1/FVC ratio for either sex (Figure 3 and Table E6 in the online supplement).

Boys in the ‘high’ FMI trajectory had lower FEV_1 (-0.14L, [-0.26; -0.01]; p-value: 0.032) than boys in the “low” FMI trajectory and there was a trend towards lower FEF_{25-75} with higher FMI trajectories (p-trend: 0.028). We did not find any statistically significant association between FMI trajectories and FEV_1 or FEF_{25-75} in girls, nor between FMI trajectories and

FVC in boys or girls. Both boys and girls who were in the highest FMI trajectory exhibited lower FEV_1/FVC ratios (Figure 3 and Table E6 in the online supplement).

All sensitivity analyses showed very similar results for LBMI (see Tables E8 to E13 in the online supplement), even after additional adjustment for physical activity and total energy intake (see Table E8 in the online supplement). For the FMI trajectories, the association between a higher FMI trajectory and a lower FEV_1/FVC ratio was maintained in all sensitivity analysis, but the associations with the other lung function parameters were more instable: first, the magnitude of the associations of FMI with FEV_1 and FEF_{25-75} (observed only in boys in the main analysis) was attenuated in some of the analyses and second, an association appeared between the 'high' FMI trajectory and post-bronchodilation FVC in girls only in some of the models.

Associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years

After adjusting for relevant confounders, there was no evidence of a consistent association between BMI trajectories and lung function growth rate (Figure 4 and Table E7 in the online supplement).

Increasing LBMI was consistently associated with higher growth rates of FVC, FEV_1 and FEF_{25-75} in both sexes, and this association exhibited a linear dose-response pattern (e.g. in boys included in the 'high' LBMI trajectory FVC increased 90.3 mL/year 95% CI [65.0; 115.7] higher than in boys in the 'low' LBMI trajectory [p-trend<0.0001]).

Boys in the 'high' (but not 'medium-low' or 'medium-high') FMI trajectory exhibited a lower growth rate of FEV_1 (-23.2mL/year, 95%IC [-40.7; -5.8]; p-value: 0.009) than boys in the 'low' FMI and there was a trend towards lower FEF_{25-75} with higher FMI trajectories (p-

trend: 0.045). We did not find any association between FMI trajectories and growth rate of FEV_1 or FEF_{25-75} in girls, nor between FMI and growth rate of FVC in boys or girls.

All sensitivity analyses showed very similar results for LBMI (see Tables E14 to E18 in the online supplement). For the FMI trajectories, the magnitude of the associations with the growth rate of FEV_1 and FEF_{25-75} (observed only in boys in the main analysis) was attenuated in some of the analyses (see Tables E14 to E18 in the online supplement) and there was a statistically significant linear trend between FMI trajectories and the growth rate of FVC in girls when we used z-scores (see Table E18 in the online supplement).

DISCUSSION

To our knowledge, this is the first study to show that body composition trajectories from childhood to adolescence relate to lung function levels at 15 years and lung function growth rates from age 8 to 15 years in a large population-based birth cohort. Specifically, we found that (i) higher LBMI was associated with higher levels and growth rates of FVC, FEV_1 and FEF_{25-75} in both sexes, and (ii) higher FMI was related to lower levels and growth rates of FEV_1 and FEF_{25-75} in boys and to a lower FEV_1/FVC ratio in both sexes.

Our finding that a higher lean body mass is related to higher lung function is consistent with observations from previous cross-sectional studies in children and adolescents (9, 14, 15). We show this association longitudinally, reducing the potential for reverse causation, and after adjustment for relevant confounders, such as physical activity, diet and pubertal status. High lean body mass may reflect increased strength of the diaphragm and chest wall during expansion and contraction during breathing (26), which could produce a greater FVC, FEV_1 and FEF_{25-75} (27). Physical activity (leading to higher levels of lean body mass) (28) could be the ultimate driver of higher lung function measures, but all associations remained stable after adjustment for physical activity (measured by accelerometer). Consequently, other mechanisms are likely to play a role.

Our study is the first to show an association between higher fat mass and increased airflow limitation (as measured by a lower FEV_1/FVC ratio) in both sexes. This association is difficult to interpret given the inconsistency of the associations between the fat mass trajectories and each of FEV_1 and FVC. Similar inconsistencies have been observed in studies on children which have used BMI as a measure of overweight/obesity; higher BMI appears to be consistently related to a lower FEV_1/FVC ratio (4, 7), but the direction of the associations between BMI with FEV_1 and FVC varies by study. One explanation could be that the fat mass component is the one that is contributing to the inconsistent results observed for BMI. We also hypothesise a mediating role of inflammation, which could explain the stronger effect of fat mass on airway calibre than on lung capacity. Since adipose tissue is a source of inflammatory mediators (29), local effects of inflammation on lung tissues could lead to reductions in airway diameter. A similar mechanism has also been proposed to explain the link between obesity and asthma (30).

Higher FMI trajectories also were related, only in boys, to lower FEV_1 and FEF_{25-75}. A previous cross-sectional study also reported an association between body adiposity (assessed through bioelectrical impedance) and FEV_1 and FVC only in boys (15). One explanation could be related to sex differences in fat distribution. Boys, unlike girls, tend to accumulate fat in the abdominal region (31), which via mechanics, may reduce the expiratory reserve volume, in turn leading to expiratory flow limitation (32).

The results of the present study have important research and public health implications. First, our study highlights the importance of assessing body composition, and not just BMI, when studying the health effects of body weight in children and adolescents. Failure to do this has likely contributed to the conflicting findings from multiple studies that have reported associations between overweight/obesity and lung function in children and adolescents (2–8). BMI, a measure based simply on height and total body mass, is unable to distinguish between

lean body mass and fat mass, and their relative proportions that vary greatly by age and sex during adolescence as a consequence of puberty (17). In fact, we found important sex differences in the levels and changes over time of lean body mass and fat mass (Figures 1 and 2). Compared to boys, girls had higher levels of fat mass at all ages and showed a higher age-related increase of FMI for all trajectories. In contrast, boys had higher levels of lean body mass at all ages and their age-related increase in LBMI was steeper than in girls. Second, our study shows that body composition in childhood and adolescence influences the development of lung function and, consequently, may affect future respiratory health. Since body composition tracks from childhood to adulthood (17) and is affected by modifiable lifestyles factors such as physical activity and diet (21, 28, 33), public health strategies promoting healthy lifestyles in early childhood may improve lung function and reduce respiratory morbidity in adult life.

A limitation of the present study is the potential selection bias produced by the fact that children included in the study were more likely to be girls, have a higher socio-economic status, a higher birth weight, a higher proportion of breastfeeding, and lower maternal smoking exposure than those excluded. Because these factors have been previously associated with lung function, our associations could be underestimates of the true associations in the general population. However, since most of the attrition occurred between birth and age 7 years, the observed associations (which are based largely on data collected from 7 to 15 years) are less likely to be affected by the loss to follow-up. Also, the regional basis of the ALSPAC cohort may not allow the generalizability of our results to populations with more ethnic variability. Finally, it is possible that using group-based trajectory modelling for identifying trajectories of body weight and composition may have smoothened the data.

Important strengths of the present research are the large sample size and the longitudinal design, which, together with the adjustment for baseline lung function (both for levels of lung

function and lung function growth rates), reduces the possibility of reverse causation. Importantly, we measured body composition using DXA, which is substantially more valid than other methods (such as bioelectrical impedance or skinfolds). Finally we had detailed information of several covariates from both the children and their parents, which allowed us to account for a wide range of potential confounders, including physical activity, diet and baseline lung function.

In conclusion, this cohort study shows that body composition in childhood and adolescence is associated with lung function in adolescence, and consequently, it may also influence respiratory health in later life. Specifically, we found that lean body mass during childhood and adolescence relates to higher lung function in adolescent boys and girls, while fat mass relates to lower lung function in boys only. This study shows that public health policies aiming to reduce respiratory morbidity should target body composition in addition to body weight.

ACKNOWLEDGMENTS

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya.

References

1. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007;30:616–622.

2. Spathopoulos D, Paraskakis E, Trypsianis G, Tsalkidis A, Arvanitidou V, Emporiadou M, Bouros D, Chatzimichael A. The effect of obesity on pulmonary lung function of school aged children in greece. *Pediatr Pulmonol* 2009;44:273–280.

3. Davidson WJ, Mackenzie-Rife KA, Witmans MB, Montgomery MD, Ball GDC, Egbogah S, Eves ND. Obesity negatively impacts lung function in children and adolescents. *Pediatr Pulmonol* 2014;49:1003–1010.

4. Forno E, Han Y-Y, Mullen J, Celedón JC. Overweight, Obesity, and Lung Function in Children and Adults—A Meta-analysis. *J Allergy Clin Immunol Pract.* 2018 Mar - Apr;6(2):570-581.

5. Bekkers MB, Wijga AH, Gehring U, Koppelman GH, de Jongste JC, Smit HA, Brunekreef B. BMI, waist circumference at 8 and 12 years of age and FVC and FEV1 at 12 years of age; the PIAMA birth cohort study. *BMC Pulm Med* 2015;15:39.

6. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax* 2003;58:1036–41.

7. Ekström S, Hallberg J, Kull I, Protudjer JLP, Thunqvist P, Bottai M, Gustafsson PM, Bergström A, Melén E. Body mass index status and peripheral airway obstruction in school-age children: a population-based cohort study. *Thorax* 2018 Jun;73(6):538-545

8. Suresh S, O'Callaghan M, Sly PD, Mamun AA. Impact of childhood anthropometry trends on adult lung function. *Chest* 2015;147:1118–1126.

9. Gonzalez-Barcala FJ, Takkouche B, Valdes L, Leis R, Alvarez-Calderon P, Cabanas R, Rodríguez Suarez JR, Tojo R. Body composition and respiratory function in healthy non-obese children. *Pediatr Int* 2007;49:553–557.

10. Kongkiattikul L, Sritippayawan S, Chomtho S, Deerojanawong J, Prapphal N. Relationship between Obesity Indices and Pulmonary Function Parameters in Obese Thai Children and Adolescents. *Indian J Pediatr* 2015;82:1112–1116.

11. Williams JE, Wells JCK, Benden C, Jaffe A, Suri R, Wilson CM, Fewtrell MS. Body composition assessed by the 4-component model and association with lung function in 6-12-y-old children with cystic fibrosis. *Am J Clin Nutr* 2010;92:1332–1343.

12. Pedreira CC, Robert RGD, Dalton V, Oliver MR, Carlin JB, Robinson P, Cameron FJ. Association of body composition and lung function in children with cystic fibrosis. *Pediatr Pulmonol* 2005;39:276–280.

13. Li, A M; Chan, D; Wong, E; Yin, J; Nelson, EAS; Fok T. The effects of obesity on pulmonary function. *Arch Dis Child* 2003;88:361–363.

14. Jensen ME, Gibson PG, Collins CE, Wood LG. Lean mass, not fat mass, is associated with lung function in male and female children with asthma. *Pediatr Res* 2014;75:93–8.

15. Wang R, Custovic A, Simpson A, Belgrave DC, Lowe LA, Murray CS. Differing associations of BMI and body fat with asthma and lung function in children. *Pediatr Pulmonol* 2014;49:1049–1057.

16. Lazarus R, Colditz G, Berkey CS, Speizer FE. Effects of body fat on ventilatory function in children and adolescents: cross-sectional findings from a random population sample of school children. *Pediatr Pulmonol* 1997;24:187–94.

17. Chumlea WC, Siervogel RM. Age and maturity related changes in body composition during adolescence into adulthood: The Fels longitudinal study. *Int J Obes* 1997;21:1167–1175.

18. Peralta GP, Fuertes E, Garcia-Aymerich J, Henderson J, Jarvis D. Lean body mass is positively associated with lung function at age 15. Presented at the European Respiratory Society Congress. Sep 9-13, 2017, Milan, Italy.

19. Boyd A, Golding J, Macleod J, Lawlor D a., Fraser A, Henderson J, Molloy L, Ness A, Ring S, Smith GD. Cohort profile: The 'Children of the 90s'-The index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2013;42:111–127.

20. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2013;42:97–110.

21. Riddoch CJ, Leary SD, Ness AR, Blair SN, Deere K, Mattocks C, Griffiths A, Davey Smith G, Tilling K. Prospective associations between objective measures of physical activity and fat mass in 12-14 year old children: the Avon Longitudinal Study of Parents and Children (ALSPAC). *BMJ* 2009;339:b4544.

22. ATS. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107–1136.

23. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010;6:109–38.

24. World Health Organization. WHO | BMI-for-age (5-19 years). *WHO* 2015;at <http://www.who.int/growthref/who2007_bmi_for_age/en/>.

25. Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *Am J Clin Nutr* 2013;98:49–56.

26. Nishimura Y, Tsutsumi M, Nakata H, Tsunenari T, Maeda H, Yokoyama M. Relationship between respiratory muscle strength and lean body mass in men with COPD. *Chest* 1995;107:1232–1236.

27. Bae JY, Jang KS, Kang S, Han DH, Yang W, Shin KO. Correlation between basic physical fitness and pulmonary function in Korean children and adolescents: a cross-sectional survey. *J Phys Ther Sci* 2015;27:2687–2692.

28. Jimenez-Pavon D, Fernandez-Vazquez A, Alexy U, Pedrero R, Cuenca-Garcia M, Polito A, Vanhelst J, Manios Y, Kafatos A, Molnar D, Sjostrom M, Moreno LA, HELENA Study Group. Association of objectively measured physical activity with body components in European adolescents. *BMC Public Health* 2013;13:667.

29. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr* 2006;83:461S–465S.

30. Boulet LP. Asthma and obesity. *Clin Exp Allergy* 2013;43:8–21.

31. Taylor RW, Grant AM, Williams SM, Goulding A. Sex Differences in Regional Body Fat Distribution From Pre- to Postpuberty. *Obesity* 2010;18:1410–1416.

32. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol* 2010;108:206–211.

33. Smith ADAC, Emmett PM, Newby PK, Northstone K. Dietary patterns and changes in body composition in children between 9 and 11 years. *Food Nutr Res* 2014;58:22769.

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Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient.

Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted.

Figure 4. Sex-specific associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years.

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient.

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Table 1. Characteristics of the participants used to assess associations of body weight and composition trajectories with lung function at 15 years

Mean (SD), Median (P_{25}-P_{75}) or n (%)	n (N=3,575)	Boys (n=1,687)	Girls (n=1,888)	p-value
Potential confounders				
Maternal social class	2,941			
Professional and intermediate	1,322	639 (46.2)	683 (43.8)	0.712
Skilled non-manual	1,179	554 (40.1)	625 (40.1)	
Skilled manual, partly, and unskilled	440	190 (13.7)	250 (16.1)	
Maternal smoking during pregnancy	3,278	260 (16.8)	290 (16.7)	0.930
Birth weight (grams)	3,381	3,485 (3,160-3,860)	3,402 (3,120-3,700)	**<0.0001**
Birth weight (z-score)§	3,366	0.5 (1.1)	0.5 (1.0)	0.686
Gestation (weeks)	3,425	40 (39-41)	40 (39-41)	**<0.0001**
Ever breastfed	3,335	1,385 (88.1)	1,521 (86.3)	0.137
Total energy intake (kcal) at 7 years	3,004	1,758 (1586-1973)	1,630 (1457-1819)	**<0.0001**
Wear-time in MVPA (minutes) at 11 years	2,955	24.4 (15.4-36.5)	15.6 (9.4-24.7)	**<0.0001**
Smoking at 14 years	2,790	42 (3.4)	109 (7.0)	**<0.0001**
Age at 15 years (years)	3,575	15.3 (15.3-15.5)	15.3 (15.3-15.5)	**0.015**
Height at 15 years (centimetres)	3,538	174.4 (169.4-179.2)	164.4 (160.6-168.6)	**<0.0001**
Height at 15 years (z-score)¶	3,538	0.4 (1.0)	0.4 (0.9)	**0.017**
Lifetime doctor-diagnosed asthma	3,573	443 (26.3)	422 (22.4)	**0.006**
Pubertal status				
Age at menarche (years)	1,701	--	12.7 (11.8-13.6)	
Voice break status at age 15 years	1,649			
Not yet started	218	218 (13.2)	--	
Starting to break	505	505 (30.6)	--	
Completely broken	926	926 (56.2)	--	
Lung function measures (Raw data)				
8 years (pre-bronchodilation)				
FVC (L)	3,078	2.0 (0.3)	1.8 (0.3)	**<0.0001**
FEV_1 (L)	3,045	1.7 (0.3)	1.6 (0.3)	**<0.0001**
FEF_{25-75} (L/s)	3,078	2.0 (0.5)	2.1 (0.5)	**0.017**
FEV_1/FVC (%)	3,045	87.3 (6.8)	89.4 (6.0)	**<0.0001**
15 years (post -bronchodilation)				
FVC (L)	3,567	4.2 (0.9)	3.3 (0.6)	**<0.0001**
FEV_1 (L)	3,433	3.8 (0.8)	3.1 (0.6)	**<0.0001**
FEF_{25-75} (L/s)	3,575	4.7 (1.2)	4.0 (1.0)	**<0.0001**
FEV_1/FVC (%)	3,433	91.1 (6.6)	93.0 (6.3)	**<0.0001**
Lung function measures (z-scores)*				
8 years (pre-bronchodilation)				
z-FVC (L)	2,807	-0.04 (1.1)	-0.03 (1.0)	0.853
z-FEV_1 (L)	2,775	-0.03 (1.0)	0.02 (1.0)	0.173
z-FEF_{25-75} (L/s)	2,807	-0.11 (1.1)	-0.13 (1.0)	0.736
z-FEV_1/FVC (%)	2,775	0.03 (1.1)	0.07 (1.0)	0.322
15 years (post -bronchodilation)				
z-FVC (L)	3,245	-0.87 (1.3)	-0.97 (1.3)	**0.024**
z-FEV_1 (L)	3,123	-0.34 (1.3)	-0.58 (1.3)	**<0.0001**
z-FEF_{25-75} (L/s)	3,253	0.16 (1.1)	0.08 (1.2)	**0.033**
z-FEV_1/FVC (%)	3,123	0.91 (1.1)	0.76 (1.1)	**0.0002**
Pre-bronchodilation lung function growth rates from age 8 to 15 years ǂ				
FVC (mL/year)	3,073	325.5 (105.8)	214.4 (72.7)	**<0.0001**
FEV_1 (mL/year)	3,013	293.8 (94.3)	200.7 (66.4)	**<0.0001**
FEF_{25-75} (mL/s·year)	3,070	327.4 (139.8)	234.2 (115.4)	**<0.0001**

§ Derived using the International Fetal and New-born Growth Consortium for the 21stCentury standards. Note that 15 children had missing values for birth weight z-score because they did not have information for gestational age, which should be included in the equation. ¶ Derived using the WHO Child Growth Standards. * Derived using the Global Lung Initiative equations. ǂ Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time of follow-up in years. Definition of abbreviations: FEF_{25-75}, forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FVC, forced vital capacity; MVPA, moderate to vigorous physical activity; P_{25}-P_{75}, 25th and 75th percentiles; SD, standard deviation; **- -,** Not relevant

p-value from the Chi-squared test, Student's t-test, or Mann-Whitney test comparing distributions across sexes. Bold: p-value <0.05

Table 2. Descriptive statistics of body weight and composition measures of the participants used to assess associations of body weight and composition trajectories with lung function at 15 years

	n (N=3,575)	Boys (n=1,687) Median (P_{25}-P_{75})	Girls (n=1,888) Median (P_{25}-P_{75})	p-value
Body weight measures				
BMI (kg/m^2)				
7 years	3,261	15.8 (14.9-16.8)	15.9 (14.9-17.3)	**0.007**
8 years	2,981	16.5 (15.5-17.9)	16.8 (15.5-18.5)	**0.007**
9 years	3,323	16.8 (15.6-18.6)	17.3 (15.8-19.2)	**<0.0001**
10 years	3,363	17.3 (15.9-19.3)	17.7 (16.1-19.9)	**0.002**
11 years	3,389	18.0 (16.5-20.4)	18.6 (16.8-21.0)	**<0.0001**
12 years	3,325	18.7 (17.1-21.0)	19.4 (17.6-21.8)	**<0.0001**
13 years	3,326	19.3 (17.7-21.5)	20.1 (18.4-22.4)	**<0.0001**
15 years	3,533	20.4 (18.8-22.5)	21.1 (19.4-23.4)	**<0.0001**
Body composition measures				
LBMI (kg/m^2)				
9 years	3,197	13.0 (12.4-13.6)	12.1 (11.5-12.7)	**<0.0001**
11 years	3,361	13.3 (12.6-14.0)	12.7 (11.9-13.5)	**<0.0001**
13 years	3,293	14.9 (13.9-16.0)	13.4 (12.7-14.2)	**<0.0001**
15 years	3,516	16.3 (15.3-17.3)	13.6 (12.8-14.3)	**<0.0001**
FMI (kg/m^2)				
9 years	3,197	3.0 (2.1-4.6)	4.3 (3.1-6.1)	**<0.0001**
11 years	3,361	3.7 (2.5-5.9)	4.9 (3.5-7.0)	**<0.0001**
13 years	3,293	3.1 (2.1-5.2)	5.7 (4.2-7.6)	**<0.0001**
15 years	3,516	2.8 (1.9-4.6)	6.5 (5.0-8.4)	**<0.0001**

Definition of abbreviations: BMI, body mass index; FMI, fat mass index; LBMI, lean body mass index; P_{25}-P_{75}, 25th and 75th percentiles
p-value from the Mann-Whitney test comparing distributions across sexes
Bold: p-value <0.05